Amyloidosis-induced Lower Gastrointestinal Bleeding in a Patient with Multiple Myeloma

Jiro HAYASHI*, Katsumichi IKI*,, Hiroshi INADA**, Masataka SATOH** and Tsukasa TSUNODA***

**Department of Gastroenterological Surgery, Kawasaki Medical School, Kurashiki 701-0192, Japan*
***Department of Surgery, Satoh Memorial Hospital, Katsuta 709-4312, Japan*

Accepted for publication on February 6, 2003

ABSTRACT. We reported a case of gastrointestinal amyloidosis associated with multiple myeloma (MM), presenting with an unusual abdominal condition causing right upper abdominal pain and hematochezia. An abdominal examination revealed a huge tender mass below the right costal margin. A barium enema examination demonstrated a filling defect in the transverse colon and abdominal computed tomography disclosed an inhomogeneous mass. There was no evidence of thrombocytopenia or a coagulation factor deficiency. A surgical specimen showed deposit of amyloid substance in the colon. As this case illustrates, the absence of systemic symptoms of amyloidosis and nonspecific radiological findings in gastrointestinal amyloidosis may make the diagnosis difficult. Therefore, we recommend that a diagnosis of amyloidosis-induced bleeding of the colon should be considered in patients with multiple myeloma with obscure hemorrhaging.

Key words : amyloidosis — bleeding — colon — multiple myeloma

Multiple myeloma (MM) represents a malignant proliferation of plasma cells derived from a single clone. Amyloidosis is a late complication of MM, occurring in 6% to 15% of patients with MM.[1] Gastrointestinal hemorrhage involvement is common in amyloidosis and is usually asymptomatic.[2] Although amyloidosis-induced gastrointestinal hemorrhage has been reported in other cases,[1-15] it appears to be extremely rare in a patient with MM.[6] Herein, we report on a patient with MM presenting with massive and life-threatening hematochezia from colonic amyloidosis, which mimicked colon cancer or metastatic disease in barium enema and computed tomography (CT) findings.

CASE REPORT

A 74-year-old woman was admitted to the hospital in October 2001, with generalized malaise and lower abdominal pain. The only positive finding on physical examination was a marked tenderness on her lower abdomen. Results of laboratory studies were as follows : erythrocyte

林 次郎, 伊木勝道, 稲田 洋, 佐藤正隆, 角田 司
e-mail : i-1130@pb3.so-net.ne.jp

sedimentation rate 111 mm/h, hemoglobin 8.8 g/dl, hematocrit 26.4%, leukocyte count 7,300/mm^3, serum creatinine 4.02 mg/dl, serum calcium 15.9 mg/dl and globulins 2.1 g/dl. Prothrombin time (PT) (13.1 second), activated partial thromboplastin time (APTT) (27.4 second), bleeding time (5 minutes), and factors VIII (180.7%), X (170.4%) and XII (101.4%) were all within normal limits. On protein electrophoresis, alpha 1, alpha 2, beta and gamma fractions were 5.7%, 18.3%, 9.9% and 7.3%, respectively. IgG, IgM, and IgA levels were 352 mg/dl, 18 mg/dl and 12 mg/dl, respectively. Immunoglobulin light chains (lambda type) were present in both serum and urine as revealed by immunoelectrophoresis. The findings were compatible with the diagnosis of MM. After the diagnosis, she received four courses of chemotherapy, including the use of cyclophosphamide and prednisolone. Hemoglobin decreased to 6.7 g/dl, creatinine decreased to 2.53 mg/dl and serum calcium decreased to 9.9 mg/dl. She showed a good response, and was doing well until February 2002, at which time an episode of upper gastrointestinal bleeding with coffee-ground vomitus and tarry stool passage occurred. Unfortunately, no definite bleeding focus could be identified by upper gastrointestinal endoscopy. She was treated with an intravenous H_2, receptor antagonist and a blood transfusion with six units of packed red blood cells. In March 2002, she began to notice periodic nausea, vomiting, abdominal pain, and repeated hematochezia. An abdominal examination revealed a huge tender mass of firm consistency below the right costal margin. Rectodigital examination disclosed bright stools with clots, which suggested that the origin of the bleeding was in the colon. A barium enema examination demonstrated that a filling defect was encountered in the oral side of the transverse colon and segmental narrowing in the anal side with the appearance of thumbprinting (Fig 1). CT revealed an inhomogeneous soft tissue mass surrounded by a hypodense layer with gas collection (Fig 2). The clinical impression was one of an intussusception

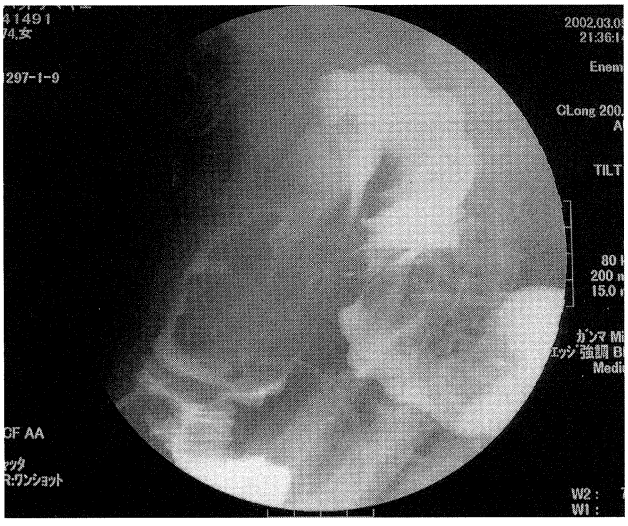

Fig 1. A barium enema revealed a filling defect with thumbprinting appearance in the transverse colon.

secondary to primary colon cancer or metastatic disease. The patient became hemodynamically unstable, and there was a significant drop in the hemoglobin/hematocrit. A surgical consultation was requested, and the patient underwent an exploratory laparotomy. at surgery, a dilated, bluish discolored transverse colon, consistent with subserosal hematoma, with bloody exudate from the colonic wall, was found. Thereafter, 500 ml of blood and blood clots were evacuated from the subserosal cavity of the colon and subsequently a right hemicolectomy was performed (Fig 3). When the colon was opened, the mucosa was found to be focally hemorrhagic along its entire length, with no discreet mass noticed.

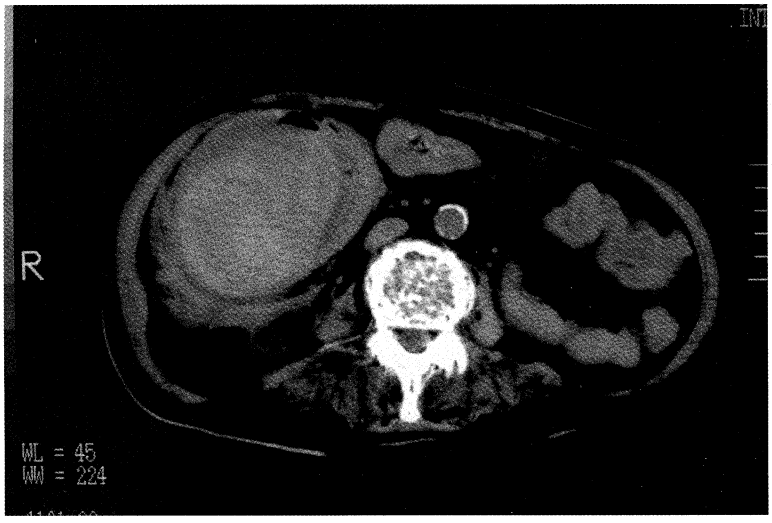

Fig 2. Computed tomography showed an inhomogeneous soft tissue mass surrounded by a hypodense layer with gas collection.

Fig 3. A large region of the transverse colon had an apparent subserosal hemorrhage, and subsequently a right hemicolectomy was performed.

Microscopic examination of hematoxylin-eosin-stained sections of the hemorrhagic mucosa disclosed ischemic necrosis and deposits of pale, amorphous eosinophilic material in the muscularis mucosa, around submucosal vessels, and infiltrating the smooth muscle of the muscularis externa (Fig 4a). Congo red staining also showed amyloid deposition in the submucosal layer and vessel walls (Fig 4b). Histochemically, potassium permanganate treatment of tissue shown to contain amyloid abolished the Congo red staining, leading us suspect AA type amyloidosis. Multiple myeloma with amyloidosis-induced bleeding of the colon was diagnosed.

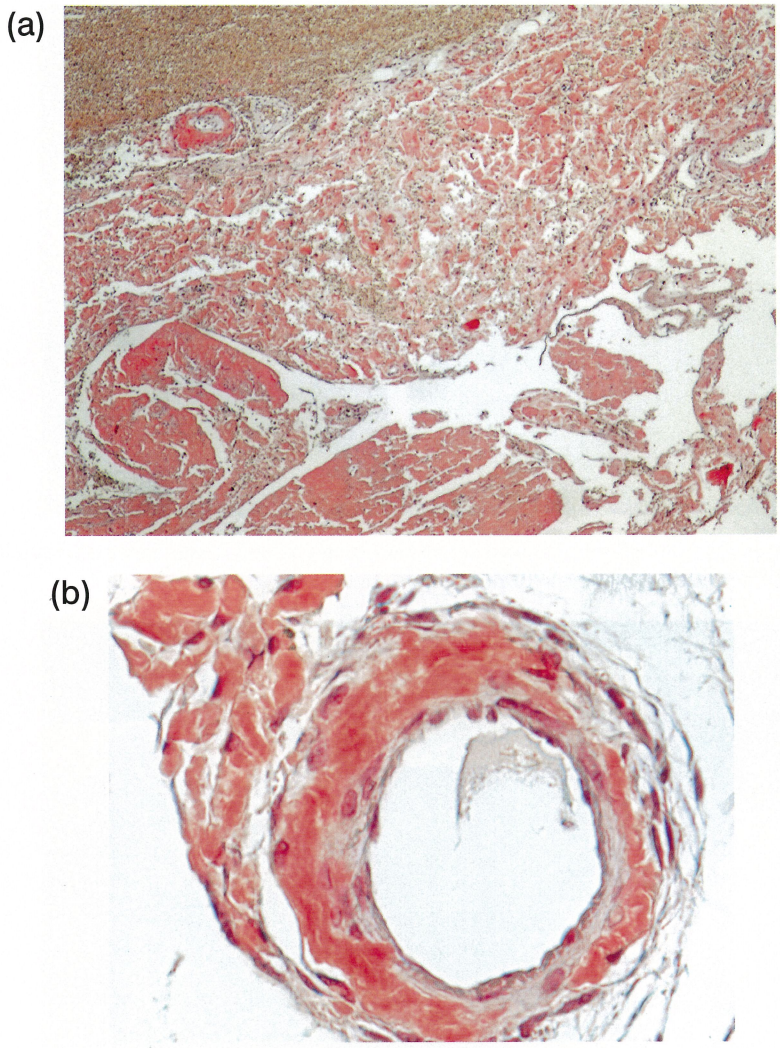

Fig 4. (a) Microscopic examination sections disclosed amorphous eosinophilic material in the muscularis mucosa, around submucosal vessels, and infiltrating the smooth muscle of the muscularis externa (H. E ; original magnification, ×40).
(b) Congo red staining also shows amyloid deposition in the submucosal layer and vessel walls (Congo red ; original magnification, ×400).

DISCUSSION

Amyloidosis has been reported to be present in 6% to 15% of patients with MM. It is extremely unlikely to complicate the course of other B-cell malignancies.[1,7-10] Althought bleeding manifestations are relatively common in the presence of amyloidosis, occurring in approximately 40% of cases,[11,12] gastrointestinal bleeding associated with MM is an extremely rare entity. Only one case of a patient with MM with duodenal bleeding induced by amyloidosis has been reported.[6] Our patient is most likely the first case of colonic bleeding induced by amyloidosis in MM.

Amyloid substance is classified into two types: amyloid L (AL) which mainly consists of light chains, and amyloid A (AA) which mainly consists of protein A. Generally, amyloidosis associated with MM is mainly of the AL type. In this case, based on the results of our histochemical examination, the source of the amyloid fibril was AA type protein. There is no reasonable explanation for the occurrence of AA type amyloidosis. Sensitivity to potassium permanganate is useful in differentiation, but, in some patients with AL, affinity for Congo red has been reduced after treatment with potassium permanganate.[13] Further studies may be needed to determine whether it will accurately distinguish AL from AA.

In MM, the bleeding tendency is due to deficiencies of factor VIII, IX, X and other vitamin K-dependent clotting factors, intravascular coagulopathy, or the deposit of amyloid substance, which causes fragility of tissue.[12,14] Impairment in fibrinogen conversion to fibrin, and increased fibrinolytic activity have also been observed in cases of MM.[12] In the present case, however, the PT, APTT and bleeding time data remained within normal limits. Therefore, it is unlikely that factor deficiencies, intravascular coagulopathy, thrombocytopenia or platelet dysfunction were responsible for this bleeding tendency. Moreover, there were no data suggestive of increased fibrinolytic activity in the present case. A gross specimen from the resected colon showed deposit of amyloid substance not only in smooth muscle with diffuse infiltration but also in the perivascular region. Therefore, deposit to the vascular system might have caused weekness in the vascular walls, and subsequently the bleeding tendency. Furthermore, the reduced motility and increased rigidity of the musculature after amyloid deposition in the intestinal wall tore the muscularis mucosa and probably resulted in massive hemorrhage.[15] The above factors might have contributed to the repeated gastrointestinal bleeding in the patient.

Gastrointestinal amyloidosis can have a variety of presentations under radiographic features, such as luminal narrowing, loss of haustrations, thickened mucosal folds, mucosal nodularity, and ulceration.[16] Recently, a better understanding of the biochemical composition of amyloid allows us to attempt to determine the type of amyloid deposited based on the radiologic or endoscopic features of amyloidosis in the gastrointestinal tract. Tada *et al*[17,18] demonstrated that the correlation between the chemical types of amyloid and radiographic features was clarified. They said that fine granular appearance was found in amyloid A protein cases, whereas multiple polypoid protrusions and thickening of valvulae conniventes were observed in amyloid AL protein cases. Our case was a very unusual one. There were

no specific radiographic evidences of amyloidosis on barium enema examination. The nonspecific radiographic appearances, such as thumbprinting appearance, which caused by focal ischemic edema, loss of haustration, and huge filling defect, probably delayed correct diagnosis. At this stage, a primary bowel tumor or metastatic disease was rightly suspected because of these radiological findings. We speculate that massive hemorrhage in the subserosal layer of the colon caused by amyloid angiopathy may be interpreted roentgenographically as a huge mass lesion. A definite diagnosis of gastrointestinal amyloidosis can only be made by tissue biopsy, and diagnosis of the amyloidosis-induced gastrointestinal bleeding — as in our patient — is usually obtained during autopsy or surgical exploration.[19]

The treatment of amyloidosis-induced gastrointestinal bleeding is difficult. Amelioration of gastrointestinal bleeding by surgical extirpation and embolotherapy has been successful in some selected patients with localized gastrointestinal amyloidosis.[20,21] A splenectomy is also suggested to stop the amyloidosis-related gastrointestinal bleeding based on the mechanism of decreasing the amyloid burden and normalization of factor X.[22,23] The prognosis of patients with amyloidosis associated with MM is quite poor. Cytotoxic agents, colchicines, steroids, and dimethylsulfoxide have all been used with some reports of improvement. Finally, amyloidosis therapy can involve surgery for localized forms, as in our patient, as well as medical therapy. For systemic forms of amyloidosis, treatment of the underlying disease is the prime concern. In conclusion, because amyloidosis can have such diverse presentation, it is often overlooked in the clinical differential diagnosis. We recommend that a diagnosis of amyloidosis should be considered in patients with MM with obscure gastrointestinal bleeding.

REFERENCES

1) Glenner GG : Amyloid deposits and amyloidosis. N Engl J Med **302** : 1333-1343, 1980
2) Fraser AG, Nicholson GI : Duodenal perforation in primary systemic amyloidosis. Gut **33** : 997-999, 1992
3) Yamamoto T, Maeda N, Kawasaki H : Hepatic failure in a case of multiple myeloma-associated amyloidosis (k-AL). J Gastroenterol **30** : 393-397, 1995
4) Coopper MM : Metastatic calcification : An unusual cause of lower intestinal hemorrhage. N Y State J Med **88** : 389-390, 1988
5) Katz JA, Metz DC, Faigel DO : Gastrointestinal bleeding from a gastric plasmacytoma. Am J Gastroenterol **89** : 642-643, 1994
6) Chang SS, Lu CL, Tsay SH, Chang FY, Lee SD : Amyloidosis-induced gastrointestinal bleeding in a patient with multiple myeloma. J Clin Gastroenterol **32** : 161-162, 2001
7) Gilat T, Spiro HM : Amyloidosis and the gut. Am J Digest Dis **13** : 619-633, 1968
8) Yamada M, Hatakeyama S, Tsukagoshi H : Gastrointestinal amyloid deposition in AL (primary or myeloma-associated) and AA (secondary) amyloidosis : Diagnostic value of gastric biopsy. Hum Pathol **16** : 1206-1211, 1985
9) Jensen K, Raynor S, Rose SG, Bailey ST, Schenken JR : Amyloid tumors of the gastrointestinal tract : A report of two cases and review of the literature. Am J Gastroenterol **80** : 784-786, 1985
10) O'Doherty DP, Neoptolemons JP, Wood KF : Place of surgery in management of amyloid disease. Br J Surg **74** : 83-88, 1987
11) Yood RA, Skinner M, Rubinow A, Talarico L, Cohen AS : Bleeding manifestations in 100 patients with amyloidosis. JAMA **249** : 1322-1324, 1983

12) Kyle RA, Greipp PR. Amyloidosis (AL) : Clinical and laboratory features in 229 cases. Mayo Clin Proc **58** : 665-683, 1983
13) Smith RRL, Hutchins GM, Moore GW, Humphrey RL : Type and distribution of pulmonary parenchymal and vascular amyloid : Correlation with cardiac amyloidosis. Am J Med **66** : 96-104, 1979
14) Glaspy JA. Hemostatic abnormalities in multiple myeloma and related disorders. Hematol Oncol Clin North Am **6** : 1301-1314, 1992
15) Keiserling E, Krober S : Massive intestinal hemorrhage associated with intestinal amyloidosis. An investigation of underlying pathologic processes. Gen Diagn Pathol **141** : 147-154, 1995
16) Trinh TD, Jones B, Fishman EK : Amyloidosis of the colon presenting as ischemic colitis : A case report and review of the literature. Gastrointest Radiol **16** : 133-136, 1991
17) Tada S, Iida M, Yao T Kawakubo K, Yao T, Fuchigami T, Okada M, Fujishima M : Gastrointestinal amyloidosis : Radiographic features by chemical types. Radiology **190** : 37-42, 1994
18) Tada S, Iida M, Yao T, Kawakubo K, Yao T, Okada M, Fujishima M : Endoscopic features in amyloidosis of the small intestine : Clinical and morphologic differences between chemical types of amyloid protein. Gastrointest Endosc **40** : 45-50, 1994
19) Levy DJ, Franklin GO, Rosenthal WS : Gastrointestinal bleeding and amyloidosis. Am J Gastroenterol **77** : 422-426, 1982
20) Long L, Mahony TD, Jewell WR : Selective amyloidosis of the jejunum. Am J Surg **109** : 217-219, 1965
21) Maeshima E, Yamada Y, Yukawa S : Massive gastrointestinal hemorrhage in a case of amyloidosis secondary to rheumatoid arthritis. Scand J Rheumatol **28** : 262-264, 1999
22) Furie B, Voo L, Mcadam KP, Furie BC : Mechanism of factor X deficiency in systemic amyloidosis. N Engl J Med **304** : 827-830, 1981
23) Greipp PR, Kyle RA, Bowie EJ : Factor X deficiency in primary amyloidosis : Resolution after splenectomy. N Engl J Med **301** : 1050-1051, 1979